PRESCRIBING INFORMATION

FLOVENT® 44 mcg
(fluticasone propionate, 44 mcg)
Inhalation Aerosol

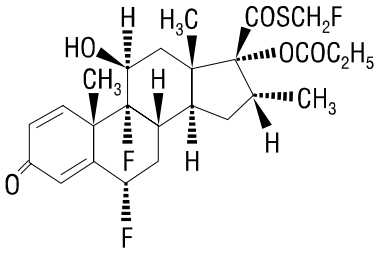
FLOVENT® 110 mcg
(fluticasone propionate, 110 mcg)
Inhalation Aerosol

FLOVENT® 220 mcg
(fluticasone propionate, 220 mcg)
Inhalation Aerosol

For Oral Inhalation Only

DESCRIPTION

The active component of FLOVENT 44 mcg Inhalation Aerosol, FLOVENT 110 mcg Inhalation Aerosol, and FLOVENT 220 mcg Inhalation Aerosol is fluticasone propionate, a glucocorticoid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLOVENT 44 mcg Inhalation Aerosol, FLOVENT 110 mcg Inhalation Aerosol, and FLOVENT 220 mcg Inhalation Aerosol are pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) in a mixture of 2 chlorofluorocarbon propellants (trichlorofluoromethane and dichlorodifluoromethane) with soya lecithin. Each actuation of the inhaler delivers 50, 125, or 250 mcg of fluticasone propionate from the valve and 44, 110, or 220 mcg, respectively, of fluticasone propionate from the actuator.

CLINICAL PHARMACOLOGY

Fluticasone propionate is a synthetic, trifluorinated glucocorticoid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

The precise mechanisms of glucocorticoid action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Glucocorticoids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of glucocorticoids may contribute to their efficacy in asthma.

Though highly effective for the treatment of asthma, glucocorticoids do not affect asthma symptoms immediately. However, improvement following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. When glucocorticoids are discontinued, asthma stability may persist for several days or longer.

Pharmacokinetics: ***Absorption:*** The activity of FLOVENT Inhalation Aerosol is due to the parent drug, fluticasone propionate. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate inhalation aerosol in healthy volunteers averaged about 30% of the dose delivered from the actuator.

Peak plasma concentrations after an 880-mcg inhaled dose ranged from 0.1 to 1.0 ng/mL.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averaged 91%. Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had approximately 2,000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

Excretion: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations: Formal pharmacokinetic studies using fluticasone propionate were not carried out in any special populations. In a clinical study using fluticasone propionate inhalation powder, trough fluticasone propionate plasma concentrations were collected in 76 males and 74 females after inhaled administration of 100 and 500 mcg twice daily. Full pharmacokinetic profiles were obtained from 7 female patients and 13 male patients at these doses, and no overall differences in pharmacokinetic behavior were found.

Drug Interactions: Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max} averaged 11.9 pg/mL [range, 10.8 to 14.1 pg/mL] and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL [range, 4.2 to 18.8 pg•hr/mL]). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range, 110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Pharmacodynamics: To confirm that systemic absorption does not play a role in the clinical response to inhaled fluticasone propionate, a double-blind clinical study comparing inhaled and oral fluticasone propionate was conducted. Doses of 100 and 500 mcg twice daily of fluticasone propionate inhalation powder were compared to oral fluticasone propionate, 20,000 mcg given once daily, and placebo for 6 weeks. Plasma levels of fluticasone propionate were detectable in all 3 active groups, but the mean values were highest in the oral group. Both doses of inhaled fluticasone propionate were effective in maintaining asthma stability and improving lung function while oral fluticasone propionate and placebo were ineffective. This demonstrates that

the clinical effectiveness of inhaled fluticasone propionate is due to its direct local effect and not to an indirect effect through systemic absorption.

The potential systemic effects of inhaled fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in patients with asthma. Fluticasone propionate given by inhalation aerosol at doses of 220, 440, 660, or 880 mcg twice daily was compared with placebo or oral prednisone 10 mg given once daily for 4 weeks. For most patients, the ability to increase cortisol production in response to stress, as assessed by 6-hour cosyntropin stimulation, remained intact with inhaled fluticasone propionate treatment. No patient had an abnormal response (peak less than 18 mcg/dL) after dosing with placebo or 220 mcg twice daily. Ten percent (10%) to 16% of patients treated with fluticasone propionate at doses of 440 mcg or more twice daily had an abnormal response as compared to 29% of patients treated with prednisone.

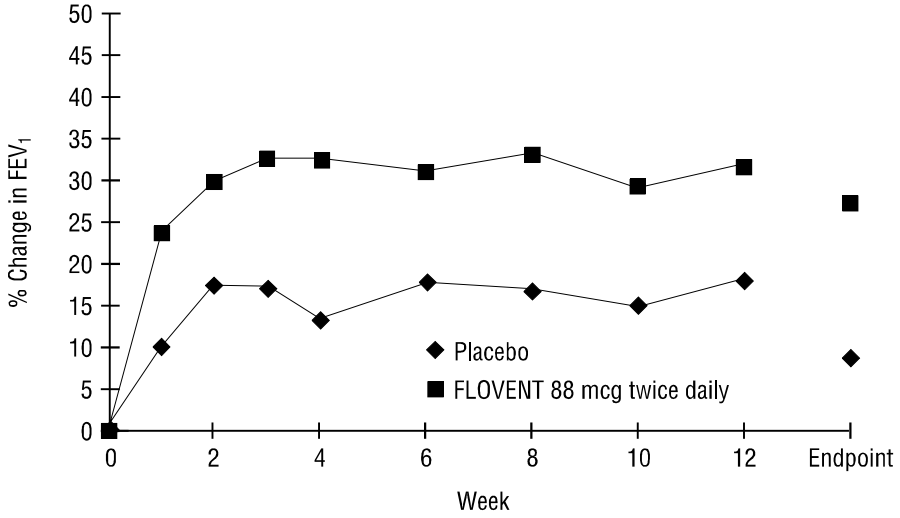
CLINICAL TRIALS

Double-blind, parallel-group, placebo-controlled, US clinical trials were conducted in 1,818 adolescent and adult patients with asthma to assess the efficacy and/or safety of FLOVENT Inhalation Aerosol in the treatment of asthma. Fixed doses ranging from 22 to 880 mcg twice daily were compared to placebo to provide information about appropriate dosing to cover a range of asthma severity. Patients with asthma included in these studies were those not adequately controlled with beta-agonists alone, those already maintained on daily inhaled corticosteroids, and those requiring oral corticosteroid therapy. In all efficacy trials, at all doses, measures of pulmonary function (forced expiratory volume in 1 second [FEV_1] and morning peak expiratory flow [AM PEF]) were statistically significantly improved as compared with placebo.

In 2 clinical trials of 660 patients with asthma inadequately controlled on bronchodilators alone, FLOVENT Inhalation Aerosol was evaluated at doses of 44 and 88 mcg twice daily. Both doses of FLOVENT Inhalation Aerosol improved asthma control significantly as compared with placebo.

Figure 1 displays results of pulmonary function tests for the recommended starting dosage of FLOVENT Inhalation Aerosol (88 mcg twice daily) and placebo from a 12-week trial in patients with asthma inadequately controlled on bronchodilators alone. Because this trial used predetermined criteria for lack of efficacy, which caused more patients in the placebo group to be withdrawn, pulmonary function results at Endpoint, which is the last evaluable FEV_1 result and includes most patients' lung function data, are also provided. Pulmonary function improved significantly with FLOVENT Inhalation Aerosol compared with placebo by the second week of treatment, and this improvement was maintained over the duration of the trial.

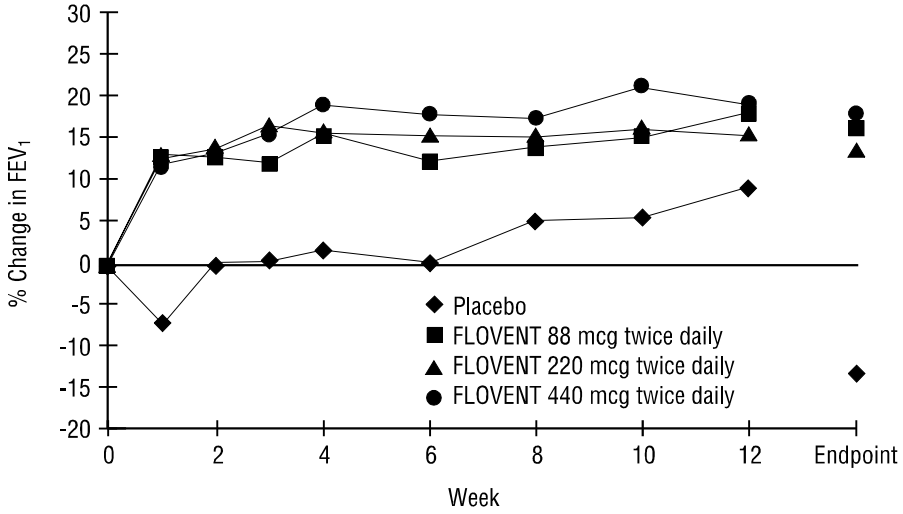
Figure 1. A 12-Week Clinical Trial in Patients Inadequately Controlled on Bronchodilators Alone: Mean Percent Change From Baseline in FEV_1 Prior to AM Dose



In clinical trials of 924 patients with asthma already receiving daily inhaled corticosteroid therapy (doses of at least 336 mcg/day of beclomethasone dipropionate) in addition to as-needed albuterol and theophylline (46% of all patients), 22- to 440-mcg twice-daily doses of FLOVENT Inhalation Aerosol were also evaluated. All doses of FLOVENT Inhalation Aerosol were efficacious when compared to placebo on major endpoints including lung function and symptom scores. Patients treated with FLOVENT Inhalation Aerosol were also less likely to discontinue study participation due to asthma deterioration (as defined by predetermined criteria for lack of efficacy including lung function and patient-recorded variables such as AM PEF, albuterol use, and nighttime awakenings due to asthma).

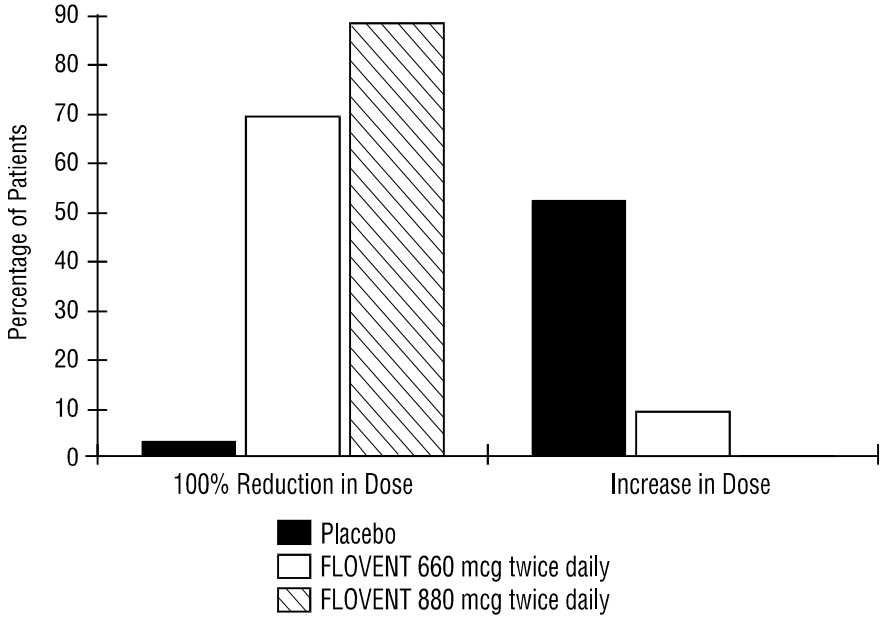
Figure 2 displays results of pulmonary function from a 12-week clinical trial in patients with asthma already receiving daily inhaled corticosteroid therapy (beclomethasone dipropionate 336 to 672 mcg/day). The mean percent change from baseline in lung function results for FLOVENT Inhalation Aerosol dosages of 88, 220, and 440 mcg twice daily and placebo are shown over the 12-week trial. Because this trial also used predetermined criteria for lack of efficacy, which caused more patients in the placebo group to be withdrawn, pulmonary function results at Endpoint are included. Pulmonary function improved significantly with FLOVENT Inhalation Aerosol compared with placebo by the first week of treatment, and the improvement was maintained over the duration of the trial. Analysis of the endpoint results that adjusted for differential withdrawal rates indicated that pulmonary function significantly improved with FLOVENT Inhalation Aerosol compared with placebo treatment. Similar improvements in lung function were seen in the other 2 trials in patients treated with inhaled corticosteroids at baseline.

Figure 2. A 12-Week Clinical Trial With Patients Already Receiving Inhaled Corticosteroids: Mean Percent Change From Baseline in FEV_1 Prior to AM Dose



In a clinical trial of 96 patients with severe asthma requiring chronic oral prednisone therapy (average baseline daily prednisone dose was 10 mg), twice-daily doses of 660 and 880 mcg of FLOVENT Inhalation Aerosol were evaluated. Both doses enabled a statistically significantly larger percentage of patients to wean successfully from oral prednisone as compared with placebo (69% of the patients on 660 mcg twice daily and 88% of the patients on 880 mcg twice daily as compared with 3% of patients on placebo). Accompanying the reduction in oral corticosteroid use, patients treated with FLOVENT Inhalation Aerosol had significantly improved lung function and fewer asthma symptoms as compared with the placebo group.

Figure 3. A 16-Week Clinical Trial in Patients Requiring Chronic Oral Prednisone Therapy: Change in Maintenance Prednisone Dose



INDICATIONS AND USAGE

FLOVENT Inhalation Aerosol is indicated for the maintenance treatment of asthma as prophylactic therapy. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

FLOVENT Inhalation Aerosol is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

FLOVENT Inhalation Aerosol is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION).

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to FLOVENT Inhalation Aerosol because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although FLOVENT Inhalation Aerosol may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to FLOVENT Inhalation Aerosol. In a trial of 96 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive reduction of prednisone dose was allowed only when lung function, symptoms, and as-needed beta-agonist use were better than or comparable to that seen before initiation of prednisone dose reduction. Lung function (FEV_1 or AM PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to FLOVENT Inhalation Aerosol may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, and arthritis.

Persons who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose,

route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

FLOVENT Inhalation Aerosol is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT Inhalation Aerosol, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with FLOVENT Inhalation Aerosol should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physicians immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with FLOVENT Inhalation Aerosol. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS

General: During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of FLOVENT Inhalation Aerosol in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with FLOVENT Inhalation Aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing FLOVENT Inhalation Aerosol.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when FLOVENT Inhalation Aerosol is administered at higher than recommended doses over prolonged periods of time. If such effects occur, fluticasone propionate inhalation aerosol should

be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of adolescents taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression if an adolescent's growth appears slowed.

The long-term effects of fluticasone propionate in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received fluticasone propionate inhalation aerosol on a continuous basis for periods of 3 years or longer. In clinical studies with patients treated for nearly 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including fluticasone propionate.

In clinical studies with inhaled fluticasone propionate, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with FLOVENT Inhalation Aerosol, but at times therapy with FLOVENT Inhalation Aerosol may need to be interrupted.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract; untreated systemic fungal, bacterial, viral or parasitic infections; or ocular herpes simplex.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS).

Information for Patients: Patients being treated with FLOVENT Inhalation Aerosol should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should use FLOVENT Inhalation Aerosol at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first day or two of

treatment; however, the full benefit may not be achieved until treatment has been administered for 1 to 2 weeks or longer. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

After inhalation, rinse the mouth with water without swallowing.

Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult the physician without delay.

For the proper use of FLOVENT Inhalation Aerosol and to attain maximum improvement, the patient should read and follow carefully the Patient's Instructions for Use accompanying the product.

Drug Interactions: Fluticasone propionate is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased mean plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when FLOVENT Inhalation Aerosol is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone propionate demonstrated no tumorigenic potential in studies of oral doses up to 1,000 mcg/kg (approximately 2 times the maximum human daily inhalation dose based on mcg/m^2) for 78 weeks in the mouse or inhalation of up to 57 mcg/kg (approximately 1/4 the maximum human daily inhalation dose based on mcg/m^2) for 104 weeks in the rat.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test when administered at high doses by the oral or subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

No evidence of impairment of fertility was observed in reproductive studies conducted in rats dosed subcutaneously with doses up to 50 mcg/kg (approximately 1/4 the maximum human daily inhalation dose based on mcg/m^2) in males and females. However, prostate weight was significantly reduced in rats.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (approximately 1/10 and 1/2 the maximum human daily inhalation dose based on mcg/m^2, respectively), revealed fetal toxicity characteristic of potent glucocorticoid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed following subcutaneous doses of 4 mcg/kg (approximately 1/25 the maximum human daily inhalation dose based on mcg/m^2). However, following oral administration of up to 300 mcg/kg (approximately 3 times the maximum human daily inhalation dose based on mcg/m^2) of fluticasone propionate to the rabbit, there were no maternal effects nor increased incidence of external, visceral, or skeletal fetal defects. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).

Less than 0.008% of the administered dose crossed the placenta following oral administration of 100 mcg/kg to rats or 300 mcg/kg to rabbits (approximately 1/2 and 3 times the maximum human daily inhalation dose based on mcg/m^2, respectively).

There are no adequate and well-controlled studies in pregnant women. FLOVENT Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral glucocorticoids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from glucocorticoids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous glucocorticoid dose and many will not need glucocorticoid treatment during pregnancy.

Nursing Mothers: It is not known whether fluticasone propionate is excreted in human breast milk. Subcutaneous administration of 10 mcg/kg tritiated drug to lactating rats (approximately 1/20 the maximum human daily inhalation dose based on mcg/m^2) resulted in measurable radioactivity in both plasma and milk. Because glucocorticoids are excreted in human milk, caution should be exercised when fluticasone propionate inhalation aerosol is administered to a nursing woman.

Pediatric Use: One hundred thirty-seven (137) patients between the ages of 12 and 16 years were treated with FLOVENT Inhalation Aerosol in the US pivotal clinical trials. The safety and effectiveness of FLOVENT Inhalation Aerosol in children below 12 years of age have not been established. Oral corticosteroids have been shown to cause a reduction in growth velocity in children and teenagers with extended use. If a child or teenager on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see PRECAUTIONS).

Geriatric Use: Five hundred seventy-four (574) patients 65 years of age or older have been treated with FLOVENT Inhalation Aerosol in US and non-US clinical trials. There were no differences in adverse reactions compared to those reported by younger patients.

ADVERSE REACTIONS

The incidence of common adverse events in Table 1 is based upon 7 placebo-controlled US clinical trials in which 1,243 patients (509 female and 734 male adolescents and adults previously treated with as-needed bronchodilators and/or inhaled corticosteroids) were treated with FLOVENT Inhalation Aerosol (doses of 88 to 440 mcg twice daily for up to 12 weeks) or placebo.

Table 1. Overall Adverse Events With >3% Incidence in US Controlled Clinical Trials With FLOVENT Inhalation Aerosol in Patients Previously Receiving Bronchodilators and/or Inhaled Corticosteroids

Adverse Event	Placebo (N = 475) %	FLOVENT 88 mcg Twice Daily (N = 488) %	FLOVENT 220 mcg Twice Daily (N = 95) %	FLOVENT 440 mcg Twice Daily (N = 185) %
Ear, nose, and throat				
Pharyngitis	7	10	14	14
Nasal congestion	8	8	16	10
Sinusitis	4	3	6	5
Nasal discharge	3	5	4	4
Dysphonia	1	4	3	8
Allergic rhinitis	4	5	3	3
Oral candidiasis	1	2	3	5
Respiratory				
Upper respiratory infection	12	15	22	16
Influenza	2	3	8	5
Neurological				
Headache	14	17	22	17
Average duration of exposure (days)	44	66	64	59

Table 1 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in groups treated with FLOVENT Inhalation Aerosol and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account.

These adverse reactions were mostly mild to moderate in severity, with ≤2% of patients discontinuing the studies because of adverse events. Rare cases of immediate and delayed hypersensitivity reactions, including urticaria and rash and other rare events of angioedema and bronchospasm, have been reported.

Systemic glucocorticoid side effects were not reported during controlled clinical trials with FLOVENT Inhalation Aerosol. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, e.g., Cushing syndrome, could occur.

Other adverse events that occurred in these clinical trials using FLOVENT Inhalation Aerosol with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Pain in nasal sinus(es), rhinitis.

Eye: Irritation of the eye(s).

Gastrointestinal: Nausea and vomiting, diarrhea, dyspepsia and stomach disorder.

Miscellaneous: Fever.

Mouth and Teeth: Dental problem.

Musculoskeletal: Pain in joint, sprain/strain, aches and pains, pain in limb.

Neurological: Dizziness/giddiness.

Respiratory: Bronchitis, chest congestion.

Skin: Dermatitis, rash/skin eruption.

Urogenital: Dysmenorrhea.

In a 16-week study in patients with asthma requiring oral corticosteroids, the effects of FLOVENT Inhalation Aerosol, 660 mcg twice daily (N = 32) and 880 mcg twice daily (N = 32), were compared with placebo. Adverse events (whether considered drug-related or nondrug-related by the investigator) reported by more than 3 patients in either group treated with FLOVENT Inhalation Aerosol and that were more common with FLOVENT than placebo are shown below:

Ear, Nose, and Throat: Pharyngitis (9% and 25%), nasal congestion (19% and 22%), sinusitis (19% and 22%), nasal discharge (16% and 16%), dysphonia (19% and 9%), pain in nasal sinus(es) (13% and 0%), Candida-like oral lesions (16% and 9%), oropharyngeal candidiasis (25% and 19%).

Respiratory: Upper respiratory infection (31% and 19%), influenza (0% and 13%).

Other: Headache (28% and 34%), pain in joint (19% and 13%), nausea and vomiting (22% and 16%), muscular soreness (22% and 13%), malaise/fatigue (22% and 28%), insomnia (3% and 13%).

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of fluticasone propionate. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate or a combination of these factors.

Ear, Nose, and Throat:| Aphonia, facial and oropharyngeal edema, hoarseness, laryngitis, and throat soreness and irritation.

Endocrine and Metabolic: Cushingoid features, growth velocity reduction in children/adolescents, hyperglycemia, osteoporosis, and weight gain.

Eye: Cataracts.

Non-Site Specific: Very rare anaphylactic reaction.

Psychiatry: Agitation, aggression, depression, and restlessness.

Respiratory: Asthma exacerbation, bronchospasm, chest tightness, cough, dyspnea, immediate bronchospasm, paradoxical bronchospasm, pneumonia, and wheeze.

Skin: Contusions, cutaneous hypersensitivity reactions, ecchymoses, and pruritus.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS: Eosinophilic Conditions).

OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS). Inhalation by healthy volunteers of a single dose of 1,760 or 3,520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. The oral and subcutaneous median lethal doses in rats and mice were >1,000 mg/kg (>2,000 times the maximum human daily inhalation dose based on mg/m^2).

DOSAGE AND ADMINISTRATION

FLOVENT Inhalation Aerosol should be administered by the orally inhaled route in patients 12 years of age and older. Individual patients will experience a variable time to onset and degree of symptom relief. Generally, FLOVENT Inhalation Aerosol has a relatively rapid onset of action for an inhaled glucocorticoid. Improvement in asthma control following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment.

After asthma stability has been achieved (see Table 2), it is always desirable to titrate to the lowest effective dosage to reduce the possibility of side effects. For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, higher dosages may provide additional asthma control. The safety and efficacy of FLOVENT Inhalation Aerosol when administered in excess of recommended dosages have not been established.

The recommended starting dosage and the highest recommended dosage of FLOVENT Inhalation Aerosol, based on prior antiasthma therapy, are listed in Table 2.

Table 2. Recommended Dosages of FLOVENT Inhalation Aerosol

Previous Therapy	Recommended Starting Dosage	Highest Recommended Dosage
Bronchodilators alone	88 mcg twice daily	440 mcg twice daily
Inhaled corticosteroids	88-220 mcg twice daily*	440 mcg twice daily
Oral corticosteroids†	880 mcg twice daily	880 mcg twice daily

* Starting dosages above 88 mcg twice daily may be considered for patients with poorer asthma control or those who have previously required doses of inhaled corticosteroids that are in the higher range for that specific agent.

NOTE: In all patients, it is desirable to titrate to the lowest effective dosage once asthma stability is achieved.

† **For Patients Currently Receiving Chronic Oral Corticosteroid Therapy:** Prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of therapy with FLOVENT Inhalation Aerosol. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency (see WARNINGS). Once prednisone reduction is complete, the dosage of fluticasone propionate should be reduced to the lowest effective dosage.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with FLOVENT Inhalation Aerosol, efficacy and safety did not differ from that in younger patients. Consequently, no dosage adjustment is recommended.

Directions for Use: Illustrated Patient's Instructions for Use accompany each package of FLOVENT Inhalation Aerosol.

HOW SUPPLIED

FLOVENT 44 mcg Inhalation Aerosol is supplied in 7.9-g canisters containing 60 metered inhalations in institutional pack boxes of 1 (NDC 0173-0497-00) and in 13-g canisters containing 120 metered inhalations in boxes of 1 (NDC 0173-0491-00). Each canister is supplied with a dark orange oral actuator with a peach strapcap and patient's instructions. Each actuation of the inhaler delivers 44 mcg of fluticasone propionate from the actuator.

FLOVENT 110 mcg Inhalation Aerosol is supplied in 7.9-g canisters containing 60 metered inhalations in institutional pack boxes of 1 (NDC 0173-0498-00) and in 13-g canisters containing 120 metered inhalations in boxes of 1 (NDC 0173-0494-00). Each canister is supplied with a dark orange oral actuator with a peach strapcap and patient's instructions. Each actuation of the inhaler delivers 110 mcg of fluticasone propionate from the actuator.

FLOVENT 220 mcg Inhalation Aerosol is supplied in 7.9-g canisters containing 60 metered inhalations in institutional pack boxes of 1 (NDC 0173-0499-00) and in 13-g canisters containing 120 metered inhalations in boxes of 1 (NDC 0173-0495-00). Each canister is supplied with a

dark orange oral actuator with a peach strapcap and patient's instructions. Each actuation of the inhaler delivers 220 mcg of fluticasone propionate from the actuator.

FLOVENT canisters are for use with FLOVENT Inhalation Aerosol actuators only. The actuators should not be used with other aerosol medications.

The correct amount of medication in each inhalation cannot be assured after 60 inhalations from the 7.9-g canister or 120 inhalations from the 13-g canister even though the canister is not completely empty. The canister should be discarded when the labeled number of actuations has been used.

Store between 2° and 30°C (36° and 86°F). Store canister with mouthpiece down. Protect from freezing temperatures and direct sunlight.

Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store at temperatures above 120°F. Keep out of reach of children. For best results, the canister should be at room temperature before use. Shake well before using.

Note: The indented statement below is required by the Federal Government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

WARNING: Contains trichlorofluoromethane and dichlorodifluoromethane, substances that harm public health and environment by destroying ozone in the upper atmosphere.

A notice similar to the above WARNING has been placed in the patient information leaflet of this product pursuant to EPA regulations.

GlaxoSmithKline
Research Triangle Park, NC 27709

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Month Year RL-

Patient's Instructions for Use

FloVent® 44 mcg 110 mcg 220 mcg
(fluticasone propionate) Inhalation Aerosol

FLOVENT® 44 mcg
(fluticasone propionate, 44 mcg)
Inhalation Aerosol

FLOVENT® 110 mcg
(fluticasone propionate, 110 mcg)
Inhalation Aerosol

FLOVENT® 220 mcg
(fluticasone propionate, 220 mcg)
Inhalation Aerosol

Please read this leaflet carefully before you start to take your medicine. It provides a summary of information on your medicine. ***For further information ask your doctor or pharmacist.***

WHAT YOU SHOULD KNOW ABOUT FLOVENT® INHALATION AEROSOL

Your doctor has prescribed FLOVENT 44 mcg Inhalation Aerosol, FLOVENT 110 mcg Inhalation Aerosol, or FLOVENT 220 mcg Inhalation Aerosol. It contains a medicine called fluticasone propionate, which is a synthetic glucocorticoid. Glucocorticoids are natural substances found in the body that help fight inflammation. They are used to treat asthma because they reduce the swelling and irritation in the walls of the small air passages in the lungs and ease breathing problems. When inhaled regularly, glucocorticoids also help to prevent attacks of asthma.

IMPORTANT POINTS TO REMEMBER ABOUT FLOVENT INHALATION AEROSOL

1. **MAKE SURE** that this medicine is suitable for you (see "BEFORE USING YOUR INHALER" below).
2. It is important that you inhale each dose as your doctor has advised. If you are not sure, ask your doctor or pharmacist.
3. Use your inhaler as directed by your doctor. **DO NOT STOP THE TREATMENT EVEN IF YOU FEEL BETTER** unless told to do so by your doctor.
4. DO NOT inhale more doses or use this inhaler more often than instructed by your doctor.
5. This medicine is NOT intended to provide rapid relief of your breathing difficulties during an asthma attack. It must be taken at regular intervals as recommended by your doctor, and not as an emergency measure.
6. Your doctor may prescribe additional medicine (such as bronchodilators) for emergency relief if an acute asthma attack occurs. Please contact your doctor if:
   - an asthma attack does not respond to the additional medicine
   - you require more of the additional medicine than usual.
7. If you also use another medicine by inhalation, you should consult your doctor for instructions on when to use it in relation to using FLOVENT Inhalation Aerosol.

BEFORE USING YOUR INHALER

TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE:

- if you are pregnant (or intending to become pregnant),
- if you are breastfeeding a baby,
- if you are allergic to FLOVENT Inhalation Aerosol, or any other orally inhaled glucocorticoid,
- if you are taking a medicine containing ritonavir (commonly used to treat HIV infection or AIDS).

In some circumstances, this medicine may not be suitable and your doctor may wish to give you a different medicine. Make sure that your doctor knows what other medicines you are taking.

USING YOUR INHALER

- Follow the instructions shown on the next few pages. If you have any problems, tell your doctor or pharmacist.
- It is important that you inhale each dose as directed by your doctor. The label will usually tell you what dose to take and how often. If it doesn't, or you are not sure, ask your doctor or pharmacist.

DOSAGE

- Use as directed by your doctor.
- It is **VERY IMPORTANT** that you follow your doctor's instructions as to how many inhalations to inhale and how often to use your inhaler.
- **DO NOT** inhale more doses or use your inhaler more often than your doctor advises.
- It may take 1 to 2 weeks or longer for this medicine to work and it is **VERY IMPORTANT THAT YOU USE IT REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU ARE FEELING BETTER** unless told to do so by your doctor.
- If you miss a dose, just take your regularly scheduled next dose when it is due. **DO NOT DOUBLE** the dose.

HOW TO USE YOUR INHALER

Read the complete instructions carefully and use only as directed.

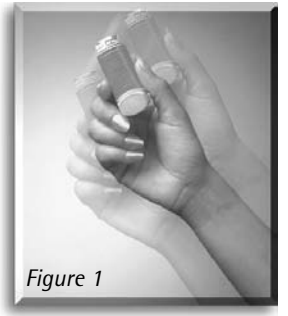
Figure 1

1 SHAKE THE INHALER WELL for 15 seconds immediately before each use *(see Figure 1).*

2 REMOVE THE CAP FROM THE MOUTHPIECE *(see Figure 2)*; the strap on the cap will stay attached to the actuator. If the strap is removed from the actuator and lost, the inhaler mouthpiece should be inspected for the presence of foreign objects before each use. Make sure the canister is fully and firmly inserted into the actuator.

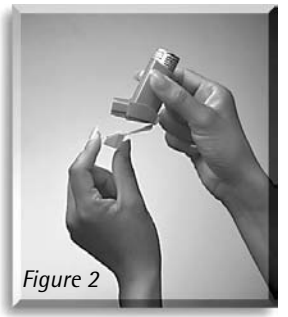
Figure 2

As with all aerosol medicine, it is recommended to "test spray" the inhaler. Do this by spraying 4 times into the air before using for the first time and when the inhaler has not been used for 4 weeks or longer. You should also spray once into the air before using when the inhaler has not been used for 1 to 3 weeks.

Avoid spraying in eyes.

3 BREATHE OUT THROUGH THE MOUTH *(see Figure 3a).* Place the mouthpiece in the mouth, holding the inhaler in the position shown in Figure 3a and closing the lips around it. Alternatively, the inhaler may be positioned 1 to 2 inches away from the open mouth *(see Figure 3b).*

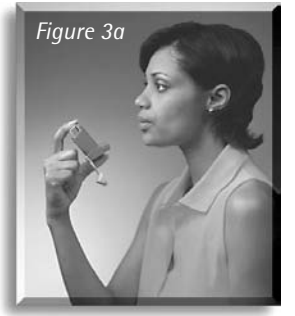
Figure 3a

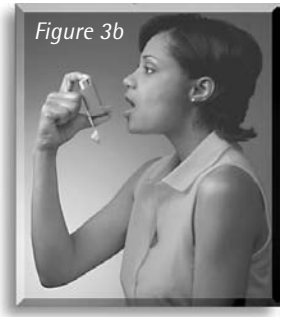
Figure 3b

4 WHILE BREATHING IN DEEPLY AND SLOWLY THROUGH THE MOUTH, PRESS DOWN FIRMLY AND FULLY ON THE TOP OF THE METAL CANISTER with your index finger *(see Figure 4).*

5 CONTINUE TO INHALE AND TRY TO HOLD YOUR BREATH FOR 10 SECONDS. Before breathing out, remove the inhaler from your mouth and release your finger from the canister.

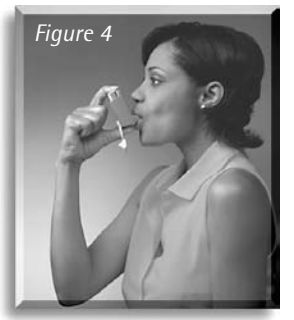
Figure 4

6 WAIT ABOUT 30 SECONDS AND SHAKE the inhaler again. Repeat steps 3 through 5 for each inhalation prescribed by your doctor.

7 REPLACE THE MOUTHPIECE CAP AFTER EACH USE.

8 RINSE YOUR MOUTH with water after you finish taking a dose. Do not swallow.

9 CLEANSE THE INHALER THOROUGHLY AND FREQUENTLY. Remove the metal canister and cleanse the plastic case and cap by rinsing thoroughly in warm, running water at least once a day. After thoroughly drying the plastic case and cap, gently replace the canister into the case with a twisting motion and replace the cap.

10 DISCARD THE CANISTER AFTER YOU HAVE USED THE LABELED NUMBER OF INHALATIONS. The correct amount of medicine in each inhalation cannot be assured after this point. You should keep track of the number of actuations used from each canister of FLOVENT Inhalation Aerosol, and discard the canister after 120 actuations from the 13-g canister or 60 actuations from the 7.9-g canister.

STORING YOUR INHALER

- Keep your inhaler **out of the reach of children.**
- Store between 2° and 30°C (36° and 86°F). Store canister with mouthpiece down. Protect from freezing temperatures and direct sunlight.
- For best results, the canister should be at room temperature before use.
- FLOVENT canisters are for use with FLOVENT Inhalation Aerosol actuators only. The actuator should not be used with other aerosol medicines.
- **DO NOT** use after the date shown as "EXP" on the label or box.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

FURTHER INFORMATION

This leaflet does not contain the complete information about your medicine. *If you have any questions, or are not sure about something, then you should ask your doctor or pharmacist.*

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

Note: The indented statement below is required by the Federal Government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFCs).

> **This product contains trichlorofluoromethane and dichlorodifluoromethane, substances which harm the environment by depleting ozone in the upper atmosphere.**

Your doctor has determined that this product is likely to help your personal health. USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR. If you have any questions about alternatives, consult with your doctor.

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Research Triangle Park, NC 27709
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July 2003 RL-2022

PRESCRIBING INFORMATION

FLOVENT® ROTADISK® 50 mcg
(fluticasone propionate inhalation powder, 50 mcg)

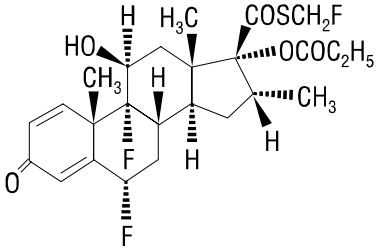
FLOVENT® ROTADISK® 100 mcg
(fluticasone propionate inhalation powder, 100 mcg)

FLOVENT® ROTADISK® 250 mcg
(fluticasone propionate inhalation powder, 250 mcg)

For Oral Inhalation Only
For Use With the DISKHALER® Inhalation Device

DESCRIPTION

The active component of FLOVENT ROTADISK 50 mcg, FLOVENT ROTADISK 100 mcg, and FLOVENT ROTADISK 250 mcg is fluticasone propionate, a corticosteroid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLOVENT ROTADISK 50 mcg, FLOVENT ROTADISK 100 mcg, and FLOVENT ROTADISK 250 mcg contain a dry powder presentation of fluticasone propionate intended for oral inhalation only. Each double-foil ROTADISK contains 4 blisters. Each blister contains a mixture of 50, 100, or 250 mcg of microfine fluticasone propionate blended with lactose (which contains milk proteins) to a total weight of 25 mg. The contents of each blister are inhaled using a specially designed plastic device for inhaling powder called the DISKHALER. After a fluticasone propionate ROTADISK is loaded into the DISKHALER, a blister containing medication is pierced and the fluticasone propionate is dispersed into the air stream created when the patient inhales through the mouthpiece.

The amount of drug delivered to the lung will depend on patient factors such as inspiratory flow. Under standardized in vitro testing, FLOVENT ROTADISK delivers 44, 88, or 220 mcg

of fluticasone propionate from FLOVENT ROTADISK 50 mcg, FLOVENT ROTADISK 100 mcg, or FLOVENT ROTADISK 250 mcg, respectively, when tested at a flow rate of 60 L/min for 3 seconds. In adult and adolescent patients with asthma, mean peak inspiratory flow (PIF) through the DISKHALER was 123 L/min (range, 88 to 159 L/min), and in pediatric patients 4 to 11 years of age with asthma, mean PIF was 110 L/min (range, 43 to 175 L/min).

CLINICAL PHARMACOLOGY

Fluticasone propionate is a synthetic, trifluorinated corticosteroid with potent anti-inflammatory activity. In vitro assays using human lung cytosol preparations have established fluticasone propionate as a human glucocorticoid receptor agonist with an affinity 18 times greater than dexamethasone, almost twice that of beclomethasone-17-monopropionate (BMP), the active metabolite of beclomethasone dipropionate, and over 3 times that of budesonide. Data from the McKenzie vasoconstrictor assay in man are consistent with these results.

The precise mechanisms of fluticasone propionate action in asthma are unknown. Inflammation is recognized as an important component in the pathogenesis of asthma. Corticosteroids have been shown to inhibit multiple cell types (e.g., mast cells, eosinophils, basophils, lymphocytes, macrophages, and neutrophils) and mediator production or secretion (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Though highly effective for the treatment of asthma, corticosteroids do not affect asthma symptoms immediately. However, improvement following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. When corticosteroids are discontinued, asthma stability may persist for several days or longer.

Pharmacokinetics: ***Absorption:*** The activity of FLOVENT ROTADISK Inhalation Powder is due to the parent drug, fluticasone propionate. Studies using oral dosing of labeled and unlabeled drug have demonstrated that the oral systemic bioavailability of fluticasone propionate is negligible (<1%), primarily due to incomplete absorption and presystemic metabolism in the gut and liver. In contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of fluticasone propionate inhalation powder in healthy volunteers averaged about 13.5% of the nominal dose.

Peak plasma concentrations after a 1,000-mcg dose of fluticasone propionate inhalation powder ranged from 0.1 to 1.0 ng/mL.

Distribution: Following intravenous administration, the initial disposition phase for fluticasone propionate was rapid and consistent with its high lipid solubility and tissue binding. The volume of distribution averaged 4.2 L/kg. The percentage of fluticasone propionate bound to human plasma proteins averaged 91%.

Fluticasone propionate is weakly and reversibly bound to erythrocytes. Fluticasone propionate is not significantly bound to human transcortin.

Metabolism: The total clearance of fluticasone propionate is high (average, 1,093 mL/min), with renal clearance accounting for less than 0.02% of the total. The only circulating metabolite detected in man is the 17β-carboxylic acid derivative of fluticasone propionate, which is formed through the cytochrome P450 3A4 pathway. This metabolite had approximately 2,000 times less affinity than the parent drug for the glucocorticoid receptor of human lung cytosol in vitro and negligible pharmacological activity in animal studies. Other metabolites detected in vitro using cultured human hepatoma cells have not been detected in man.

In a multiple-dose drug interaction study, coadministration of fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

In a drug interaction study, coadministration of fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased fluticasone propionate concentrations, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol.

Excretion: Following intravenous dosing, fluticasone propionate showed polyexponential kinetics and had a terminal elimination half-life of approximately 7.8 hours. Less than 5% of a radiolabeled oral dose was excreted in the urine as metabolites, with the remainder excreted in the feces as parent drug and metabolites.

Special Populations: Formal pharmacokinetic studies using fluticasone propionate were not carried out in any special populations. In a clinical study using fluticasone propionate inhalation powder, trough fluticasone propionate plasma concentrations were collected in 76 males and 74 females after inhaled administration of 100 and 500 mcg twice daily. Full pharmacokinetic profiles were obtained from 7 female patients and 13 male patients at these doses, and no overall differences in pharmacokinetic behavior were found.

Plasma concentrations of fluticasone propionate were measured 20 and 40 minutes after dosing from 29 children aged 4 to 11 years who were taking either 50 or 100 mcg twice daily of fluticasone propionate inhalation powder. Plasma concentration values ranged from below the limit of quantitation (25 pg/mL) to 117 pg/mL (50-mcg dose) or 154 pg/mL (100-mcg dose). In a study with adults taking the 100-mcg twice-daily dose, the plasma concentrations observed ranged from below the limit of quantitation to 73.1 pg/mL. The median fluticasone propionate plasma concentrations for the 100-mcg dose in children was 58.7 pg/mL; in adults the median plasma concentration was 39.5 pg/mL.

Drug Interactions: Fluticasone propionate is a substrate of cytochrome P450 3A4. Coadministration of fluticasone propionate and the highly potent cytochrome P450 3A4 inhibitor ritonavir is not recommended based upon a multiple-dose, crossover drug interaction study in 18 healthy subjects. Fluticasone propionate aqueous nasal spray (200 mcg once daily) was coadministered for 7 days with ritonavir (100 mg twice daily). Plasma fluticasone propionate concentrations following fluticasone propionate aqueous nasal spray alone were undetectable (<10 pg/mL) in most subjects, and when concentrations were detectable peak levels (C_{max} averaged 11.9 pg/mL [range, 10.8 to 14.1 pg/mL] and $AUC_{(0-\tau)}$ averaged 8.43 pg•hr/mL [range, 4.2 to 18.8 pg•hr/mL]). Fluticasone propionate C_{max} and $AUC_{(0-\tau)}$ increased to 318 pg/mL (range,

110 to 648 pg/mL) and 3,102.6 pg•hr/mL (range, 1,207.1 to 5,662.0 pg•hr/mL), respectively, after coadministration of ritonavir with fluticasone propionate aqueous nasal spray. This significant increase in plasma fluticasone propionate exposure resulted in a significant decrease (86%) in plasma cortisol area under the plasma concentration versus time curve (AUC).

Caution should be exercised when other potent cytochrome P450 3A4 inhibitors are coadministered with fluticasone propionate. In a drug interaction study, coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in increased plasma fluticasone propionate exposure and reduced plasma cortisol AUC, but had no effect on urinary excretion of cortisol.

In another multiple-dose drug interaction study, coadministration of orally inhaled fluticasone propionate (500 mcg twice daily) and erythromycin (333 mg 3 times daily) did not affect fluticasone propionate pharmacokinetics.

Pharmacodynamics: To confirm that systemic absorption does not play a role in the clinical response to inhaled fluticasone propionate, a double-blind clinical study comparing inhaled and oral fluticasone propionate was conducted. Doses of 100 and 500 mcg twice daily of fluticasone propionate inhalation powder were compared to oral fluticasone propionate, 20,000 mcg given once daily, and placebo for 6 weeks. Plasma levels of fluticasone propionate were detectable in all 3 active groups, but the mean values were highest in the oral group. Both doses of inhaled fluticasone propionate were effective in maintaining asthma stability and improving lung function while oral fluticasone propionate and placebo were ineffective. This demonstrates that the clinical effectiveness of inhaled fluticasone propionate is due to its direct local effect and not to an indirect effect through systemic absorption.

The potential systemic effects of inhaled fluticasone propionate on the hypothalamic-pituitary-adrenal (HPA) axis were also studied in patients with asthma. Fluticasone propionate given by inhalation aerosol at doses of 220, 440, 660, or 880 mcg twice daily was compared with placebo or oral prednisone 10 mg given once daily for 4 weeks. For most patients, the ability to increase cortisol production in response to stress, as assessed by 6-hour cosyntropin stimulation, remained intact with inhaled fluticasone propionate treatment. No patient had an abnormal response (peak serum cortisol <18 mcg/dL) after dosing with placebo or fluticasone propionate 220 mcg twice daily. For patients treated with 440, 660, and 880 mcg twice daily, 10%, 16%, and 12%, respectively, had an abnormal response as compared to 29% of patients treated with prednisone.

In clinical trials with fluticasone propionate inhalation powder, using doses up to and including 250 mcg twice daily, occasional abnormal short cosyntropin tests (peak serum cortisol <18 mcg/dL) were noted in patients receiving fluticasone propionate or placebo. The incidence of abnormal tests at 500 mcg twice daily was greater than placebo. In a 2-year study carried out in 64 patients randomized to fluticasone propionate 500 mcg twice daily or placebo, 1 patient receiving fluticasone propionate (4%) had an abnormal response to 6-hour cosyntropin infusion at 1 year; repeat testing at 18 months and 2 years was normal. Another patient receiving

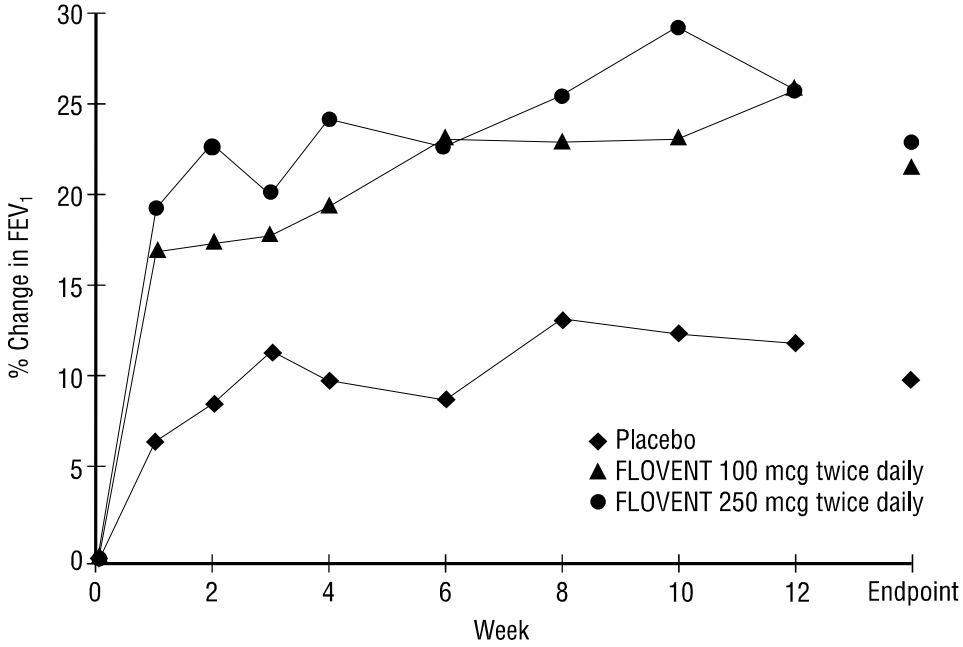
fluticasone propionate (5%) had an abnormal response at 2 years. No patient on placebo had an abnormal response at 1 or 2 years.

CLINICAL TRIALS

Double-blind, parallel-group, placebo-controlled, US clinical trials were conducted in 1,197 adolescent and adult patients with asthma to assess the efficacy and safety of FLOVENT ROTADISK in the treatment of asthma. Fixed doses of 50, 100, 250, and 500 mcg twice daily were compared to placebo to provide information about appropriate dosing to cover a range of asthma severity. Patients with asthma included in these studies were those not adequately controlled with beta-agonists alone, and those already maintained on daily inhaled corticosteroids. In these efficacy trials, at all doses, measures of pulmonary function (forced expiratory volume in 1 second [FEV_1] and morning peak expiratory flow [AM PEF]) were statistically significantly improved as compared with placebo. All doses were delivered by inhalation of the contents of 1 or 2 blisters from the DISKHALER twice daily.

Figure 1 displays results of pulmonary function tests for 2 recommended dosages of FLOVENT ROTADISK (100 and 250 mcg twice daily) and placebo from a 12-week trial in 331 adolescent and adult patients with asthma (baseline FEV_1 = 2.63 L/sec) inadequately controlled on bronchodilators alone. Because this trial used predetermined criteria for lack of efficacy, which caused more patients in the placebo group to be withdrawn, pulmonary function results at Endpoint, which is the last evaluable FEV_1 result and includes most patients' lung function data, are also provided. Pulmonary function at both dosages of FLOVENT ROTADISK improved significantly compared with placebo by the first week of treatment, and this improvement was maintained over the duration of the trial.

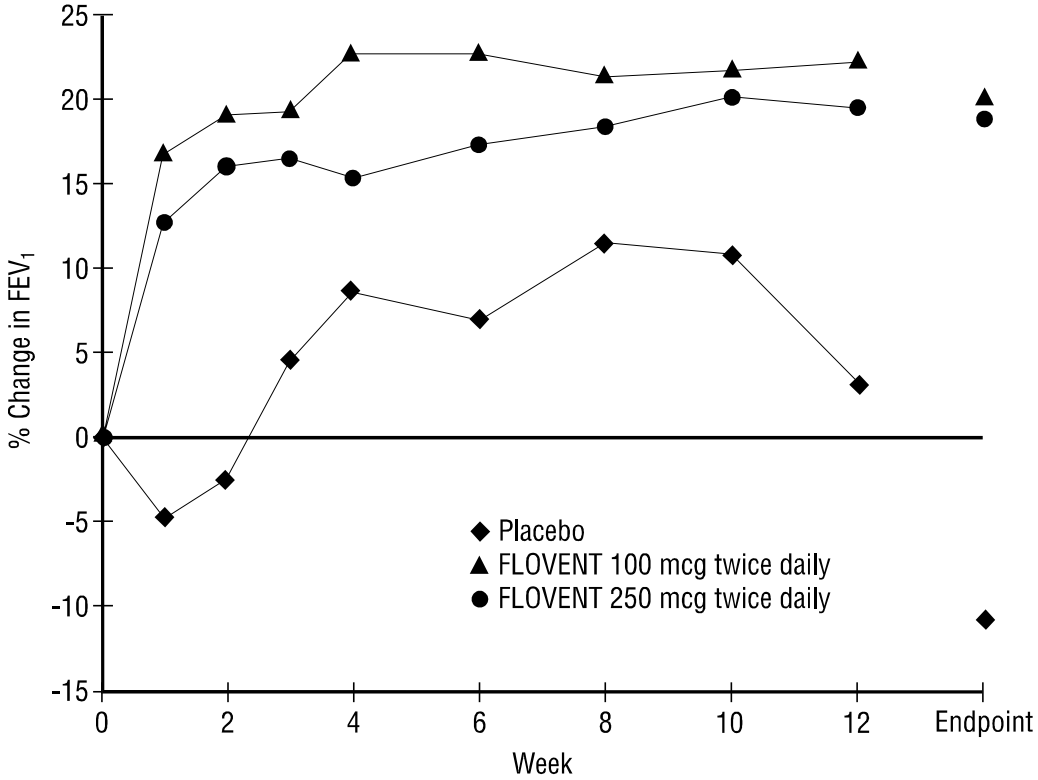
Figure 1. A 12-Week Clinical Trial in Patients Inadequately Controlled on Bronchodilators Alone: Mean Percent Change From Baseline in FEV_1 Prior to AM Dose



In a second clinical study of 75 patients, 500 mcg twice daily was evaluated in a similar population. In this trial FLOVENT ROTADISK significantly improved pulmonary function as compared with placebo.

Figure 2 displays results of pulmonary function tests for 2 recommended dosages of FLOVENT ROTADISK (100 and 250 mcg twice daily) and placebo from a 12-week trial in 342 adolescent and adult patients with asthma (baseline FEV_1 = 2.49 L/sec) already receiving daily inhaled corticosteroid therapy (≥336 mcg/day of beclomethasone dipropionate or ≥800 mcg/day of triamcinolone acetonide) in addition to as-needed albuterol and theophylline (38% of all patients). Because this trial also used predetermined criteria for lack of efficacy, which caused more patients in the placebo group to be withdrawn, pulmonary function results at Endpoint are included. Pulmonary function at both dosages of FLOVENT ROTADISK improved significantly compared with placebo by the first week of treatment, and the improvement was maintained over the duration of the trial.

Figure 2. A 12-Week Clinical Trial in Patients Already Receiving Inhaled Corticosteroids: Mean Percent Change From Baseline in FEV_1 Prior to AM Dose



In a second clinical study of 139 patients, treatment with 500 mcg twice daily was evaluated in a similar patient population. In this trial FLOVENT ROTADISK significantly improved pulmonary function as compared with placebo.

In the 4 trials described above, all dosages of FLOVENT ROTADISK were efficacious; however, at higher dosages, patients were less likely to discontinue study participation due to asthma deterioration (as defined by predetermined criteria for lack of efficacy including lung function and patient-recorded variables such as AM PEF, albuterol use, and nighttime awakenings due to asthma).

In a clinical trial of 96 patients with severe asthma requiring chronic oral prednisone therapy (average baseline daily prednisone dose was 10 mg), fluticasone propionate given by inhalation aerosol at doses of 660 and 880 mcg twice daily was evaluated. Both doses enabled a statistically significantly larger percentage of patients to wean successfully from oral prednisone as compared with placebo (69% of the patients on 660 mcg twice daily and 88% of the patients on 880 mcg twice daily as compared with 3% of patients on placebo). Accompanying the reduction in oral corticosteroid use, patients treated with fluticasone propionate had significantly improved lung function and fewer asthma symptoms as compared with the placebo group. These data were obtained from a clinical study using fluticasone propionate inhalation aerosol; no

direct assessment of the clinical comparability of equal nominal doses for the FLOVENT ROTADISK and FLOVENT Inhalation Aerosol formulations in this population has been conducted.

Pediatric Experience: In a 12-week, placebo-controlled clinical trial of 263 patients aged 4 to 11 years inadequately controlled on bronchodilators alone (baseline morning peak expiratory flow = 200 L/min), fluticasone propionate inhalation powder doses of 50 and 100 mcg twice daily significantly improved morning peak expiratory flow (28% and 34% change from baseline at Endpoint, respectively) compared to placebo (11% change). In a second placebo-controlled, 52-week trial of 325 patients aged 4 to 11 years, approximately half of whom were receiving inhaled corticosteroids at baseline, doses of fluticasone propionate inhalation powder of 50 and 100 mcg twice daily improved lung function by the first week of treatment, and the improvement continued over 1 year compared to placebo. In both studies, patients on active treatment were significantly less likely to discontinue treatment due to lack of efficacy.

INDICATIONS AND USAGE

FLOVENT ROTADISK is indicated for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of these patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

FLOVENT ROTADISK is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

FLOVENT ROTADISK is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of these preparations contraindicates their use (see DESCRIPTION and ADVERSE REACTIONS: Observed During Clinical Practice: *Non-Site Specific*).

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to FLOVENT ROTADISK because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although FLOVENT ROTADISK may provide control of asthma symptoms during these episodes, in

recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to FLOVENT ROTADISK. In a clinical trial of 96 patients, prednisone reduction was successfully accomplished by reducing the daily prednisone dose by 2.5 mg on a weekly basis during transfer to inhaled fluticasone propionate. Successive reduction of prednisone dose was allowed only when lung function, symptoms, and as-needed beta-agonist use were better than or comparable to that seen before initiation of prednisone dose reduction. Lung function (FEV_1 or AM PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to FLOVENT ROTADISK may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, arthritis.

Persons who are on drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package

inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

FLOVENT ROTADISK is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

As with other inhaled asthma medications, bronchospasm may occur with an immediate increase in wheezing after dosing. If bronchospasm occurs following dosing with FLOVENT ROTADISK, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with FLOVENT ROTADISK should be discontinued and alternative therapy instituted.

Patients should be instructed to contact their physicians immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment with FLOVENT ROTADISK. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS

General: During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Fluticasone propionate will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since fluticasone propionate is absorbed into the circulation and can be systemically active at higher doses, the beneficial effects of FLOVENT ROTADISK in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. A relationship between plasma levels of fluticasone propionate and inhibitory effects on stimulated cortisol production has been shown after 4 weeks of treatment with FLOVENT Inhalation Aerosol. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing FLOVENT ROTADISK.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when FLOVENT ROTADISK is administered at higher than recommended doses over prolonged periods of time. If such effects occur, FLOVENT ROTADISK should be reduced slowly, consistent with accepted procedures for reducing systemic corticosteroids and for management of asthma symptoms.

A reduction of growth velocity in children or adolescents may occur as a result of poorly controlled asthma or from the therapeutic use of corticosteroids, including inhaled corticosteroids. A 52-week placebo-controlled study to assess the potential growth effects of

FLOVENT ROTADISK at 50 and 100 mcg twice daily was conducted in the US in 325 prepubescent children (244 males and 81 females) 4 to 11 years of age. The mean growth velocities at 52 weeks observed in the intent-to-treat population were 6.32 cm/year in the placebo group (n = 76), 6.07 cm/year in the 50-mcg group (n = 98), and 5.66 cm/year in the 100-mcg group (n = 89). An imbalance in the proportion of children entering puberty between groups and a higher dropout rate in the placebo group due to poorly controlled asthma may be confounding factors in interpreting these data. A separate subset analysis of children who remained prepubertal during the study revealed growth rates at 52 weeks of 6.10 cm/year in the placebo group (n = 57), 5.91 cm/year in the 50-mcg group (n = 74), and 5.67 cm/year in the 100-mcg group (n = 79). The clinical significance of these growth data is not certain. In children 8.5 years of age, the mean age of children in this study, the range for expected growth velocity is: boys – 3rd percentile = 3.8 cm/year, 50th percentile = 5.4 cm/year, and 97th percentile = 7.0 cm/year; girls – 3rd percentile = 4.2 cm/year, 50th percentile = 5.7 cm/year, and 97th percentile = 7.3 cm/year. The effects of long-term treatment of children with inhaled corticosteroids, including fluticasone propionate, on final adult height are not known. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route, and weigh the benefits of corticosteroid therapy against the possibility of growth suppression if growth appears slowed. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

The long-term effects of fluticasone propionate in human subjects are not fully known. In particular, the effects resulting from chronic use of fluticasone propionate on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. Some patients have received inhaled fluticasone propionate on a continuous basis for periods of 3 years or longer. In clinical studies with patients treated for 2 years with inhaled fluticasone propionate, no apparent differences in the type or severity of adverse reactions were observed after long- versus short-term treatment.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including fluticasone propionate.

In clinical studies with inhaled fluticasone propionate, the development of localized infections of the pharynx with *Candida albicans* has occurred. When such an infection develops, it should be treated with appropriate local or systemic (i.e., oral antifungal) therapy while remaining on treatment with FLOVENT ROTADISK, but at times therapy with FLOVENT ROTADISK may need to be interrupted.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculous infections of the respiratory tract; untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated

with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see ADVERSE REACTIONS).

Information for Patients: Patients being treated with FLOVENT ROTADISK should receive the following information and instructions. This information is intended to aid them in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Patients should use FLOVENT ROTADISK at regular intervals as directed. Results of clinical trials indicated significant improvement may occur within the first day or two of treatment; however, the full benefit may not be achieved until treatment has been administered for 1 to 2 weeks or longer. The patient should not increase the prescribed dosage but should contact the physician if symptoms do not improve or if the condition worsens.

Patients should be warned to avoid exposure to chickenpox or measles and, if they are exposed, to consult their physicians without delay.

For the proper use of FLOVENT ROTADISK and to attain maximum improvement, the patient should read and follow carefully the Patient's Instructions for Use accompanying the product.

Drug Interactions: Fluticasone propionate is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations (see CLINICAL PHARMACOLOGY: Drug Interactions). During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

In a placebo-controlled, crossover study in 8 healthy volunteers, coadministration of a single dose of orally inhaled fluticasone propionate (1,000 mcg) with multiple doses of ketoconazole (200 mg) to steady state resulted in increased plasma fluticasone propionate exposure, a reduction in plasma cortisol AUC, and no effect on urinary excretion of cortisol. Caution should be exercised when FLOVENT ROTADISK is coadministered with ketoconazole and other known potent cytochrome P450 3A4 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Fluticasone propionate demonstrated no tumorigenic potential in mice at oral doses up to 1,000 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults and approximately 10 times the maximum recommended daily inhalation dose in children on a mcg/m^2 basis) for 78 weeks

or in rats at inhalation doses up to 57 mcg/kg (approximately 1/4 the maximum recommended daily inhalation dose in adults and comparable to the maximum recommended daily inhalation dose in children on a mcg/m^2 basis) for 104 weeks.

Fluticasone propionate did not induce gene mutation in prokaryotic or eukaryotic cells in vitro. No significant clastogenic effect was seen in cultured human peripheral lymphocytes in vitro or in the mouse micronucleus test when administered at high doses by the oral or subcutaneous routes. Furthermore, the compound did not delay erythroblast division in bone marrow.

No evidence of impairment of fertility was observed in reproductive studies conducted in male and female rats at subcutaneous doses up to 50 mcg/kg (approximately 1/5 the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). Prostate weight was significantly reduced at a subcutaneous dose of 50 mcg/kg.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Subcutaneous studies in the mouse and rat at 45 and 100 mcg/kg, respectively (approximately 1/10 and 1/3, respectively, the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis), revealed fetal toxicity characteristic of potent corticosteroid compounds, including embryonic growth retardation, omphalocele, cleft palate, and retarded cranial ossification.

In the rabbit, fetal weight reduction and cleft palate were observed at a subcutaneous dose of 4 mcg/kg (approximately 1/30 the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). However, no teratogenic effects were reported at oral doses up to 300 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) of fluticasone propionate. No fluticasone propionate was detected in the plasma in this study, consistent with the established low bioavailability following oral administration (see CLINICAL PHARMACOLOGY).

Fluticasone propionate crossed the placenta following oral administration of 100 mcg/kg to rats or 300 mcg/kg to rabbits (approximately 1/3 and 2 times, respectively, the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. FLOVENT ROTADISK should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nursing Mothers: It is not known whether fluticasone propionate is excreted in human breast milk. Subcutaneous administration to lactating rats of 10 mcg/kg tritiated fluticasone propionate (approximately 1/25 the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) resulted in measurable radioactivity in milk. Because other corticosteroids are excreted in

human milk, caution should be exercised when FLOVENT ROTADISK is administered to a nursing woman.

Pediatric Use: Two hundred fourteen (214) patients 4 to 11 years of age and 142 patients 12 to 16 years of age were treated with FLOVENT ROTADISK in US clinical trials. The safety and effectiveness of FLOVENT ROTADISK Inhalation Powder in children below 4 years of age have not been established.

Inhaled corticosteroids, including fluticasone propionate, may cause a reduction in growth in children and adolescents (see PRECAUTIONS). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma.

Geriatric Use: Safety data have been collected on 280 patients (FLOVENT® DISKUS® N = 83, FLOVENT ROTADISK N = 197) 65 years of age or older and 33 patients (FLOVENT DISKUS N = 14, FLOVENT ROTADISK N = 19) 75 years of age or older who have been treated with fluticasone propionate inhalation powder in US and non-US clinical trials. There were no differences in adverse reactions compared to those reported by younger patients. In addition, there were no apparent differences in efficacy between patients 65 years of age or older and younger patients. Fifteen patients 65 years of age or older and 1 patient 75 years of age or older were included in the efficacy evaluation of US clinical studies.

ADVERSE REACTIONS

The incidence of common adverse events in Table 1 is based upon 6 placebo-controlled clinical trials in which 1,384 patients ≥4 years of age (520 females and 864 males) previously treated with as-needed bronchodilators and/or inhaled corticosteroids were treated with FLOVENT ROTADISK (doses of 50 to 500 mcg twice daily for up to 12 weeks) or placebo.

Table 1. Overall Adverse Events With >3% Incidence in Controlled Clinical Trials With FLOVENT ROTADISK in Patients ≥4 Years Previously Receiving Bronchodilators and/or Inhaled Corticosteroids

Adverse Event	Placebo (N = 438) %	FLOVENT 50 mcg Twice Daily (N = 255) %	FLOVENT 100 mcg Twice Daily (N = 331) %	FLOVENT 250 mcg Twice Daily (N = 176) %	FLOVENT 500 mcg Twice Daily (N = 184) %
Ear, nose, and throat					
Pharyngitis	7	6	8	8	13
Nasal congestion	5	4	4	7	7
Sinusitis	4	5	4	6	4
Rhinitis	4	4	9	2	3
Dysphonia	0	<1	4	6	4
Oral candidiasis	1	3	3	4	11
Respiratory					
Upper respiratory infection	13	16	17	22	16
Influenza	2	3	3	3	4
Bronchitis	2	4	2	1	2
Other					
Headache	11	11	9	14	15
Diarrhea	1	2	2	0	4
Back problems	<1	<1	1	1	4
Fever	3	4	4	2	2
Average duration of exposure (days)	53	77	68	78	60

Table 1 includes all events (whether considered drug-related or nondrug-related by the investigator) that occurred at a rate of over 3% in any of the groups treated with FLOVENT ROTADISK and were more common than in the placebo group. In considering these data, differences in average duration of exposure should be taken into account.

These adverse reactions were mostly mild to moderate in severity, with <2% of patients discontinuing the studies because of adverse events. Rare cases of immediate and delayed hypersensitivity reactions, including rash and other rare events of angioedema and bronchospasm, have been reported.

Other adverse events that occurred in these clinical trials using FLOVENT ROTADISK with an incidence of 1% to 3% and that occurred at a greater incidence than with placebo were:

Ear, Nose, and Throat: Otitis media, tonsillitis, nasal discharge, earache, laryngitis, epistaxis, sneezing.

Eye: Conjunctivitis.

Gastrointestinal: Abdominal pain, viral gastroenteritis, gastroenteritis/colitis, abdominal discomfort.

Miscellaneous: Injury.

Mouth and Teeth: Mouth irritation.

Musculoskeletal: Sprain/strain, pain in joint, disorder/symptoms of neck, muscular soreness, aches and pains.

Neurological: Migraine, nervousness.

Respiratory: Chest congestion, acute nasopharyngitis, dyspnea, irritation due to inhalant.

Skin: Dermatitis, urticaria.

Urogenital: Dysmenorrhea, candidiasis of vagina, pelvic inflammatory disease, vaginitis/vulvovaginitis, irregular menstrual cycle.

There were no clinically relevant differences in the pattern or severity of adverse events in children compared with those reported in adults.

FLOVENT Inhalation Aerosol (660 or 880 mcg twice daily) was administered for 16 weeks to patients with asthma requiring oral corticosteroids. Adverse events reported more frequently in these patients compared to patients not on oral corticosteroids included sinusitis, nasal discharge, oropharyngeal candidiasis, headache, joint pain, nausea and vomiting, muscular soreness, malaise/fatigue, and insomnia.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during postapproval use of fluticasone propionate in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These experiences have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to fluticasone propionate or a combination of these factors.

Ear, Nose, and Throat: Aphonia, facial and oropharyngeal edema, hoarseness, and throat soreness and irritation.

Endocrine and Metabolic: Cushingoid features, growth velocity reduction in children/adolescents, hyperglycemia, osteoporosis, and weight gain.

Eye: Cataracts.

Non-Site Specific: Very rare anaphylactic reaction, very rare anaphylactic reaction in patients with severe milk protein allergy.

Psychiatry: Agitation, aggression, depression, and restlessness.

Respiratory: Asthma exacerbation, bronchospasm, chest tightness, cough, immediate bronchospasm, paradoxical bronchospasm, pneumonia, and wheeze.

Skin: Contusions, ecchymoses, and pruritus.

Eosinophilic Conditions: In rare cases, patients on inhaled fluticasone propionate may present with systemic eosinophilic conditions, with some patients presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of

fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established (see PRECAUTIONS: Eosinophilic Conditions).

OVERDOSAGE

Chronic overdosage may result in signs/symptoms of hypercorticism (see PRECAUTIONS). Inhalation by healthy volunteers of a single dose of 4,000 mcg of fluticasone propionate inhalation powder or single doses of 1,760 or 3,520 mcg of fluticasone propionate inhalation aerosol was well tolerated. Fluticasone propionate given by inhalation aerosol at doses of 1,320 mcg twice daily for 7 to 15 days to healthy human volunteers was also well tolerated. Repeat oral doses up to 80 mg daily for 10 days in healthy volunteers and repeat oral doses up to 20 mg daily for 42 days in patients were well tolerated. Adverse reactions were of mild or moderate severity, and incidences were similar in active and placebo treatment groups. The oral and subcutaneous median lethal doses in mice and rats were >1,000 mg/kg (>2,000 and >4,100 times, respectively, the maximum recommended daily inhalation dose in adults and >9,600 and >19,000 times, respectively, the maximum recommended daily inhalation dose in children on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION

FLOVENT ROTADISK should be administered by the orally inhaled route in patients 4 years of age and older. Individual patients will experience a variable time to onset and degree of symptom relief. Generally, FLOVENT ROTADISK has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhaled administration of fluticasone propionate can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment.

After asthma stability has been achieved (see Table 2), it is always desirable to titrate to the lowest effective dosage to reduce the possibility of side effects. Dosages as low as 50 mcg twice daily have been shown to be effective in some patients. For patients who do not respond adequately to the starting dosage after 2 weeks of therapy, higher dosages may provide additional asthma control. The safety and efficacy of FLOVENT ROTADISK when administered in excess of recommended dosages have not been established.

Rinsing the mouth after inhalation is advised.

The recommended starting dosage and the highest recommended dosage of FLOVENT ROTADISK, based on prior anti-asthma therapy, are listed in Table 2.

Table 2. Recommended Dosages of FLOVENT ROTADISK

Previous Therapy	Recommended Starting Dosage	Highest Recommended Dosage
Adults and Adolescents		
Bronchodilators alone	100 mcg twice daily	500 mcg twice daily
Inhaled corticosteroids	100-250 mcg twice daily*	500 mcg twice daily
Oral corticosteroids†	1,000 mcg twice daily‡	1,000 mcg twice daily‡
Children 4 to 11 Years		
Bronchodilators alone	50 mcg twice daily	100 mcg twice daily
Inhaled corticosteroids	50 mcg twice daily	100 mcg twice daily

* Starting dosages above 100 mcg twice daily for adults and adolescents and 50 mcg twice daily for children 4 to 11 years of age may be considered for patients with poorer asthma control or those who have previously required doses of inhaled corticosteroids that are in the higher range for that specific agent.

NOTE: In all patients, it is desirable to titrate to the lowest effective dosage once asthma stability is achieved.

† **For Patients Currently Receiving Chronic Oral Corticosteroid Therapy:** Prednisone should be reduced no faster than 2.5 mg/day on a weekly basis, beginning after at least 1 week of therapy with FLOVENT ROTADISK. Patients should be carefully monitored for signs of asthma instability, including serial objective measures of airflow, and for signs of adrenal insufficiency (see WARNINGS). Once prednisone reduction is complete, the dosage of fluticasone propionate should be reduced to the lowest effective dosage.

‡ This dosing recommendation is based on clinical data from a study conducted using FLOVENT Inhalation Aerosol. No clinical trials have been conducted in patients on oral corticosteroids using FLOVENT ROTADISK; no direct assessment of the clinical comparability of equal nominal doses for FLOVENT ROTADISK and FLOVENT Inhalation Aerosol in this population has been conducted.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see PRECAUTIONS) have been treated with FLOVENT ROTADISK, efficacy and safety did not differ from that in younger patients. Consequently, no dosage adjustment is recommended.

Directions for Use: Illustrated Patient's Instructions for Use accompany each package of FLOVENT ROTADISK.

HOW SUPPLIED

FLOVENT ROTADISK 50 mcg is a circular double-foil pack containing 4 blisters of the drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of 15 ROTADISKS and 1 dark orange and peach DISKHALER inhalation device (NDC 0173-0511-00).

FLOVENT ROTADISK 100 mcg is a circular double-foil pack containing 4 blisters of the drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of 15 ROTADISKS and 1 dark orange and peach DISKHALER inhalation device (NDC 0173-0509-00).

FLOVENT ROTADISK 250 mcg is a circular double-foil pack containing 4 blisters of the drug. Fifteen (15) ROTADISKS are packaged in a white polypropylene tube, and the tube is packaged in a plastic-coated, moisture-protective foil pouch. A carton contains the foil pouch of 15 ROTADISKS and 1 dark orange and peach DISKHALER inhalation device (NDC 0173-0504-00).

Store at controlled room temperature (see USP), 20° to 25°C (68° to 77°F) in a dry place. Keep out of reach of children. Do not puncture any fluticasone propionate ROTADISK blister until taking a dose using the DISKHALER.

Use the ROTADISK blisters within 2 months after opening of the moisture-protective foil overwrap or before the expiration date, whichever comes first. Place the sticker provided with the product on the tube and enter the date the foil overwrap is opened and the 2-month use date.

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Research Triangle Park, NC 27709

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Month Year RL-

Patient's Instructions for Use

FLOVENT® ROTADISK® 50 mcg
(fluticasone propionate inhalation powder, 50 mcg)

FLOVENT® ROTADISK® 100 mcg
(fluticasone propionate inhalation powder, 100 mcg)

FLOVENT® ROTADISK® 250 mcg
(fluticasone propionate inhalation powder, 250 mcg)

Please read this leaflet carefully before you start to take your medicine. It provides a summary of information on your medicine. ***For further information ask your doctor or pharmacist.***

What You Should Know About FLOVENT® ROTADISK®

Your doctor has prescribed FLOVENT ROTADISK 50 mcg, FLOVENT ROTADISK 100 mcg, or FLOVENT ROTADISK 250 mcg. Each ROTADISK® contains a medicine called fluticasone propionate, which is a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. They are used to treat asthma because they reduce the swelling and irritation in the walls of the small air passages in the lungs and ease breathing problems. When inhaled regularly, corticosteroids also help to prevent attacks of asthma.

Important Points to Remember About FLOVENT ROTADISK

1. **MAKE SURE** that this medicine is suitable for you (see "Before Using Your FLOVENT ROTADISK" below).
2. It is important that you inhale each dose as your doctor has advised. If you are not sure, ask your doctor or pharmacist.
3. Use your ROTADISK as directed by your doctor. **DO NOT STOP THE TREATMENT EVEN IF YOU FEEL BETTER** unless told to do so by your doctor.
4. DO NOT inhale more doses or use the ROTADISK more often than instructed by your doctor.
5. This medicine is NOT intended to provide rapid relief of your breathing difficulties during an asthma attack. It must be taken at regular intervals as recommended by your doctor, and not as an emergency measure.
6. Your doctor may prescribe additional medicine (such as bronchodilators) for emergency relief if an acute asthma attack occurs. Please contact your doctor if:
   - an asthma attack does not respond to the additional medicine
   - you require more of the additional medicine than usual.
7. If you also use another medicine by inhalation, you should consult your doctor for instructions on when to use it in relation to using FLOVENT ROTADISK.

Before Using Your FLOVENT ROTADISK

TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE:
- If you are pregnant (or intending to become pregnant),
- If you are breastfeeding a baby,
- If you are allergic to FLOVENT ROTADISK, any other medicines, or food products. In some circumstances, this medicine may not be suitable and your doctor may wish to give you a different medicine. Make sure that your doctor knows what other medicines you are taking.
- If you are taking a medicine containing ritonavir (commonly used to treat HIV infection or AIDS).

Using Your FLOVENT ROTADISK

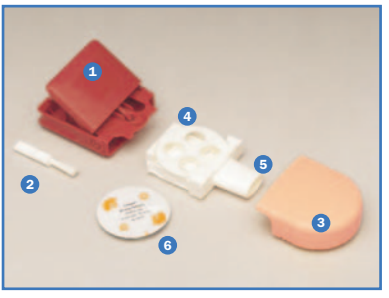
- Follow the instructions below. If you have any problems, tell your doctor or pharmacist.
- It is important that you inhale each dose as directed by your doctor. The label will usually tell you what dose to take and how often. If it doesn't, or you are not sure, ask your doctor or pharmacist.

DOSAGE
- Use as directed by your doctor.
- It is **VERY IMPORTANT** that you follow your doctor's instructions as to how many inhalations to inhale and how often to use your FLOVENT ROTADISK.
- **DO NOT** inhale more doses or use your FLOVENT ROTADISK more often than your doctor advises.
- It may take 1 to 2 weeks or longer for this medicine to work and it is **VERY IMPORTANT THAT YOU USE IT REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU ARE FEELING BETTER** unless told to do so by your doctor.
- If you miss a dose, just take your regularly scheduled next dose when it is due. **DO NOT DOUBLE** the dose.

How to Use Your FLOVENT ROTADISK

This leaflet shows you how to use FLOVENT ROTADISK. The medicine comes in small circular foil disks. There are 4 blisters around the edge of each disk, and these blisters each contain a measured dose of your medicine as a powder that you breathe by using a specially designed plastic device called the DISKHALER®. The medicine is available in several different strengths, and your doctor has chosen the one most suitable for you.

The DISKHALER has a number of parts:
1. outer body with a hinged lid and piercing needle
2. cleaning brush that fits into a space at the rear of the body
3. mouthpiece cover
4. white wheel on which the disk is placed
5. white sliding tray with mouthpiece fitted to the wheel
6. foil disk



Loading a Disk into the DISKHALER®

Figure 1

1. Remove the mouthpiece cover and check to make sure that the mouthpiece is clean *(see Figure 1)*. Inspect the mouthpiece for the presence of foreign objects before each use.
2. Hold the corners of the white tray and pull out gently until you can see all the plastic ridges on the sides of the tray *(see Figure 2)*.
3. Put your finger and thumb on the ridges, squeeze inward, and gently pull the tray out of the body of the DISKHALER *(see Figure 3)*.
4. Place a disk on the wheel with the numbers facing up, and then slide the tray back into the DISKHALER *(see Figure 4)*.

Figure 2

Figure 3

Figure 4

Getting Ready for the First Dose

5. Hold the corners of the tray *(see Figure 5)* and slide the tray out and in. This will rotate the disk.

6. Continue until the number "4" appears in the small window *(see Figure 6)*. The disk is now ready for use. As you use each dose, the number of doses remaining is shown in the window.

Figure 5

Figure 6

Opening the Blister to Release a Dose

7. Keep the DISKHALER level. Lift up the back of the lid as far as it will go until it is fully upright *(see Figure 7)*. (**IMPORTANT:** The lid must be raised until fully upright to pierce both the top and bottom of the blister.) Then close the lid. The DISKHALER is now ready for use.

Figure 7

Inhaling Your Medicine

8. Breathe out as far as comfortable *(see Figure 8)*.

9. Keep the DISKHALER level and raise it to your mouth. Place the mouthpiece between your teeth and close your lips firmly around it but do not bite down on it *(see Figure 9)*. **Do not cover** the small air holes on either side of the mouthpiece.

10. **Breathe in through your mouth steadily and as deeply as you can.**

11. Hold your breath and remove the DISKHALER from your mouth *(see Figure 10)*. Continue to hold your breath for up to 10 seconds or as long as is comfortable.

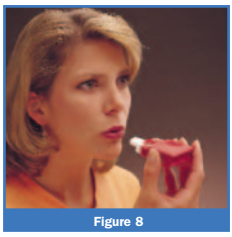


Figure 8

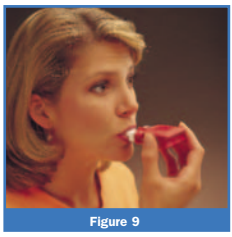


Figure 9

Figure 10

Getting Ready for the Next Dose

Figure 11

12. Turn the disk to the next number ("3") by gently pulling out the tray and pushing it in once *(see Figure 11)*. **Do not** pierce the blister until you are ready to take the next dose.

When you need to take another dose, repeat steps 7 through 12.

Always replace the mouthpiece cover after use.

Replacing the Disk When it is Empty

Each disk has 4 blisters. As you use up each blister, the blister numbers appearing in the small window of the tray will count backwards (i.e., "4", "3", "2", "1"). When the number "4" reappears after you have taken 4 inhalations from the DISKHALER, the disk is empty and should be replaced. To take out the old disk and put in the new one, repeat steps 2 through 4.

Cleaning Your DISKHALER

Clean your DISKHALER at least once a week as follows:
1. Remove the tray from the body of the DISKHALER.
2. Hold the wheel between your forefinger and thumb and pull upwards to separate it from the tray.
3. There is a brush in the small space under the lid at the rear of the body of the DISKHALER. Brush away any powder left behind on the parts of the DISKHALER.
4. Replace the wheel and push it down firmly until it snaps into place.
5. Replace the tray and mouthpiece cover.

You may also separate the parts of the DISKHALER as described above and rinse them with warm water. Let the parts air dry before putting back together.

Storing Your FLOVENT ROTADISK

- **Keep out of reach of children.**
- Store at 20° to 25°C (68° to 77°F) in a **dry place.**
- **Use the ROTADISK blisters within 2 months after opening of the moisture-protective foil overwrap or before the expiration date, whichever comes first. Place the sticker provided with the product on the tube containing the ROTADISK blisters and fill in the date you opened the foil overwrap and the 2-month use date.**
- Do not puncture any fluticasone propionate ROTADISK blister until taking a dose using the DISKHALER.

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

FURTHER INFORMATION

This leaflet does not contain the complete information about your medicine. *If you have any questions, or are not sure about something, then you should ask your doctor or pharmacist.*

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

Your doctor has determined that this product is likely to help your personal health. **USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.** If you have any questions about alternatives, consult with your doctor.

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